Prognosis in monoclonal proteinaemia

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2 Serum interleukin-6 has no discriminatory role in paraproteinaemia nor a prognostic role in multiple myeloma

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Abstract

We determined interleukin-6 (IL-6) in serum of 212 well-defined patients with newly diagnosed paraproteinaemia and evaluated its discriminatory value and its prognostic role in multiple myeloma (MM). Results were compared with serum neural cell adhaesion molecule and β-2-microglobulin, both established prognostic MM markers. Paraproteinaemia related diagnoses were: MM (60), other haematological diseases (46), solid tumours (35), auto-immune diseases (17) and monoclonal gammopathy of unknown significance (MGUS) (54). IL-6 ranges in all diagnostic groups overlapped widely and did not serve as a discriminatory marker in newly diagnosed paraproteinaemia even when patients with infection or fever (42) were excluded. In MM high IL-6 levels (≥50 pg/ml) were not associated with a shorter survival ($p=0.24$). We compared our results with 20 published studies on serum IL-6 in paraproteinaemia and/or MM. IL-6 data have to be related to the assay used (bio- or immunoassay) and to the status of MM (newly diagnosed, during therapy, progressive disease). We conclude that serum IL-6 is not specific for paraproteinaemia-related diseases and will not serve as a reliable discriminatory or prognostic marker in paraproteinaemia and MM.

Introduction

Monoclonal gammopathy or paraproteinaemia is not synonymous with multiple myeloma (MM). At first presentation a diagnosis of MM, plasmacytoma, amyloidosis or other haematological malignancy is made in only 37% of these patients[1]. The majority of patients with a newly diagnosed paraprotein, does not fulfil the diagnostic criteria for MM and hence are classified as having monoclonal gammopathy of undetermined significance (MGUS). Follow-up of MGUS patients for more then twenty years has shown that MM, amyloidosis or other haematological malignancies arise in 24%, demonstrating that lifelong follow-up is mandatory[1].
For newly diagnosed patients with paraproteinaemia the need is felt for an easy (serum) parameter to distinguish MM from other causes of paraproteinaemia. Interleukin-6 (IL-6) is a potent *in vitro* and *in vivo* growth factor for human myeloma cells and has therefore received much attention as a possible tumour-, disease activity-, and prognostic marker in MM and other causes of paraproteinaemia[2]. Recently, the diagnostic value of serum neural cell adhesion molecule (NCAM) in newly diagnosed patients with MM and other well-defined monoclonal gammopathies of different causes was demonstrated. The specificity was excellent (97%) but the sensitivity was low (52%)[3]. We decided to test the diagnostic value of serum IL-6 in paraproteinaemia and its prognostic value in MM in the same group of patients. Moreover we included the results with NCAM, C-reactive protein (CRP) and β-2-microglobulin (β2M) in the analysis of these patients. In addition, we compared our IL-6 data with all published series available.

Patients and methods

Patients: From 1991 till 1993 a population-based registry on paraproteinaemia was carried out in the region of the Comprehensive Cancer Center West (CCCW). All patients with newly diagnosed paraproteinaemia and/or multiple myeloma in the Midwestern part of The Netherlands (1,6 million inhabitants and 15 hospitals in 1992) were reported by clinical chemists, internists, haematologists, pathologists and other physicians. Information on patient characteristics (age, sex, performance status), laboratory tests results (haemoglobin, leukocyte- and thrombocyte counts, creatinin, calcium, albumen, total protein, paraprotein type and concentration in serum and urine), and results of bone marrow and skeletal x-rays were obtained. The paraprotein-related diagnosis, comorbidity and therapy were recorded. A serum sample obtained at registration was centrally stored at -80 ºC. Follow-up was done at least once yearly. In total, 1464 patients have been registered. The setup and contents of this registry have been described[4]. Paraproteins were either detected by agarose or cellulose-acetate electrophoresis depending on the method used in each hospital where

the patient was first seen. For inclusion in the registry each paraprotein had to be confirmed by immunotyping (immunofixation). Serum was available from 867 patients. Out of this series, 212 sera were selected in whom all diagnostic tests had been performed and a paraprotein-related diagnosis was available[3].
Multiple myeloma was diagnosed in 60 patients, other haematological diseases in 46 patients, solid tumour in 35, auto-immune disease in 17 and MGUS in 54 patients. Different stages among the MM patients were: indolent myeloma 9 cases, stage I 13 cases, stage II 4 cases and stage III 34 cases. Other haematological malignancies consisted of lymphoproliferative diseases: 39 (15 immunocytoma, 18 other B-cell non-Hodgkin's lymphoma, 4 B-cell chronic lymphocytic leukaemia, 2 Hodgkin's disease) and myeloproliferative diseases: 7 (6 myelodysplastic syndrome, 1 promyelocytic leukaemia). According to the criteria of the British Columbia Cancer Agency (BCCA) the diagnosis of MM was made when at least two of the following criteria were present: paraprotein in serum and/or urine, lytic bone lesion(s), or more than 10% plasma cells in bone marrow cytology[5;6]. A paraprotein in serum (but not in urine), with more than 10% plasma cells in cytology, in the absence of symptoms, anaemia, leucocytopenia, thrombocytopenia, hypercalciaemia, renal failure due to myeloma or lytic bone lesions was diagnosed as indolent MM[3;5]. Any paraprotein without indication of MM or other (haematological) malignancies, or auto-immune disease with less than 10% plasma cells in bone marrow cytology was termed MGUS[3].
Laboratory Methods: Serum samples stored at -80 ºC were thawed and shipped on ice to the Marburg University (Germany) where NCAM and IL-6 determinations were done. For IL-6 determinations an enzyme linked immunoabsorbent assay (LD Zytokit IL-6 ELISA, LD Labor Diagnostika Heiden, Germany) was used with a sensitivity of 1 pg/ml. The analyses of β2M, CRP and NCAM have been described before[3]. Interassay coefficients of variation for IL-6 were less than 8%, for NCAM 2-8%, for β2M 7-10% and for CRP less than 8%. Upper normal serum values were 20 U/ml for NCAM, 3 mg/l for β2M and less than 10 mg/l for CRP. As median values and ranges for serum IL-6 differ among normal control groups no reference values were available (see also Table 3). IL-6, NCAM, CRP and β2M were determined in blinded samples. Other laboratory results were extracted from the registry.
Statistics: The comparison of median values of laboratory parameters for different diagnostic categories was done using Mann-Whitney's test (2 groups) or Kruskall-Wallis test (more than 2 groups). Survival was calculated from diagnosis to death (event) or to being alive at last follow-up (censoring). Survival curves were made using the Kaplan Meier methods and compared with the log-rank test. Analyses were performed using SPSS/PC+; data were entered in a database using SPSS Data Entry II (both SPSS Inc, Chicago, IL).
Literature search: For the period January 1966 to May 1999 we searched the medical literature in Medline using the items: 'paraproteinaemia', 'monoclonal gammopathy', 'interleukin-6' and 'multiple myeloma'. All studies on serum IL-6 in patients with paraproteinaemia and/or MM were reviewed.

Results

Interleukin-6: Serum IL-6 was measurable in all 212 patients studied. The median values and ranges for IL-6, NCAM, CRP and β2M are shown in Table 1. Figure 1 is a graphic display of the individual IL-6 values grouped by diagnostic category. The median levels of IL-6 showed significant differences between the diagnostic categories (Kruskall Wallis test, $p<0.001$), but overlapped widely and none had a characteristic range. IL-6 values correlated with CRP ($r=0.42$; $p<0.0001$), but not with NCAM, osteolysis and β2M. At presentation 42 patients (lymphoproliferative (9), solid tumour (6), auto-immune disease (2), MGUS (15), MM I (6), MM III (4)) had either a documented infection or fever without a known cause. Excluding these from analysis did not make any difference (Table 1, $p=0.005$).

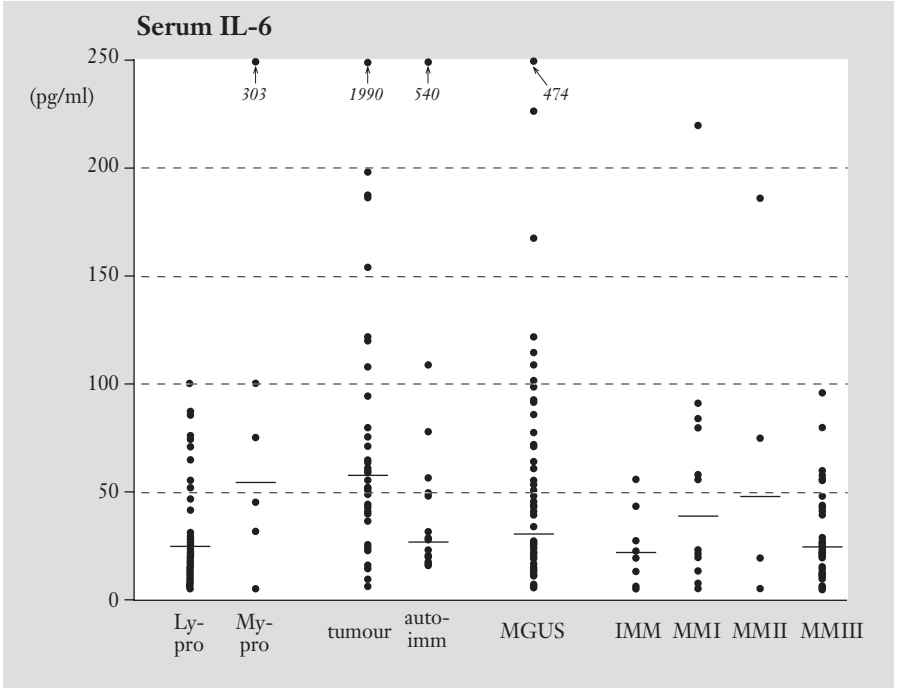

Figure 1. **Range of serum IL-6 in all diagnostic categories. Median levels of serum IL-6 are depicted as bars. Outliers are represented by an arrow and accompanied by the actual value.**

Ly-pro: lymphoproliferative disease;
My-pro: myeloproliferative disease;
tumour: solid tumour;
auto-imm: auto-immune disease;
IMM: indolent MM.

Table 1. **Median serum value (ranges) of IL-6, NCAM, CRP, β2M.**

Category	N	NCAM (U/ml)	CRP (mg/l)	β2M (mg/l)	Serum IL-6 (pg/ml) unselected	Serum IL-6 (pg/ml) no infection/fever	N
Lymphoproliferative	39	9.2 (1.5-30.2)	6 (2-236)	3.4 (1.5-14.7)	25 (6-100)	22 (7-100)	30
Myeloproliferative	7	4.1 (2.7-12.7)	33 (4-236)	7.4 (2.4-22.2)	55 (6-303)	55 (6-303)	7
solid tumour	35	5.1 (1.0-17.4)	50 (2-335)	3.2 (2.0-16.0)	58 (7-1,990)	58 (7-1,990)	29
auto-immune	17	5.1 (1.7-24.0)	6 (2-158)	2.5 (1.6-16.1)	29 (18-540)	27 (18-540)	14
MGUS	54	7.1 (2.4-19.2)	25 (2-155)	3.2 (1.1-9.3)	31 (7-474)	28 (7-474)	39
IMM	9	16.4 (5.7-110.4)	4 (2-163)	2.5 (1.3-5.7)	22 (6-56)	22 (6-56)	9
MM I	13	10.3 (5.5-181.3)	8 (2-334)	3.9 (2.0-9.4)	39 (6-220)	22 (6-58)	7
MM II	4	31.3 (3.0-85.2)	16 (5-97)	5.8 (3.4-7.4)	48 (6-186)	48 (6-186)	4
MM III	34	24.3 (2.4-219.7)	4 (2-116)	5.9 (2.0-48.6)	25 (6-96)	25 (6-96)	30

For practical clinical purposes all diagnostic categories were combined to three major groups; non-MM (lymphoproliferative, myeloproliferative, solid tumour, and autoimmune disease), MGUS and MM (IMM, MM I, MM II, MM III). Median serum IL-6 values in non-MM and MGUS were significantly higher than in patients with MM (Table 2). IL-6 values in MGUS were higher than in MM though this difference disappeared after excluding all patients with a documented infection or fever at diagnosis. β2M and NCAM levels were significantly higher in MM compared to non-MM and MGUS whereas CRP was higher in the latter two (Table 2).

Serum IL-6 and survival in patients with MM: We investigated whether high IL-6 serum levels at diagnosis were of prognostic significance for survival in patients with MM. Median time of follow-up was 44 months (range 0-74 months). Patients with MM and initial high values of IL-6 (≥50 pg/ml) showed a median survival of 23 months compared to 33 months in MM-patients with lower IL-6 values (<50 pg/ml) though this was not statistically significant (p=0.24; Figure 2). Even at several other cut-off values (25, 75, and 100 pg/ml) no significant correlation of serum IL-6 at diagnosis with survival was found. Not surprisingly an elevated CRP (≥10 mg/l) was also not associated with shorter survival. In contrast, elevated values of the established prognostic serum marker β2M (>3 mg/l) were significantly (p=0.013) associated with a worse prognosis. Median survival time in patients with elevated β2M was less than half the median survival time in patients with normal serum values (22 months vs. 47 months; Figure 2). Serum NCAM proved to be a relevant prognostic factor as well. Patients with MM and a high NCAM level (≥20 U/ml) at diagnosis had a median survival time of 22 months whereas normal levels were associated with a median survival of 54 months (p=0.04; Figure 2).

Table 2. **Patients grouped as non-MM, MGUS and MM, comparison of median serum values of IL-6, NCAM, CRP, and β2M.**

Category	N	NCAM (U/ml)	CRP (mg/l)	β2M (mg/l)	Serum IL-6 (pg/ml) unselected	Serum IL-6 (pg/ml) no infection/fever	N
non-MM	98	6.7 (1.0-30,2)	17 (2-335)	3.4 (1.5-22.2)	43 (6-1,990)	37 (6-1,990)	81
MGUS	54	7.1 (2.4-19.2)	25 (2-155)	3.2 (1.1-9.3)	31 (7-474)	28 (7-474)	39
MM	60	20.0 (2.4-219.7)	5 (2-334)	4.4 (1.3-48.6)	24 (6-220)	23 (6-186)	50
Mann-Whitney							
non-MM vs MGUS		p=0.8	p=0.7	p=0.2	p=0.9	p=0.5	
non-MM vs MM		p=0.00001*	p=0.003*	p=0.02*	p=0.01*	p=0.01*	
MGUS vs MM		p=0.00001*	p=0.04*	p=0.002*	p=0.03*	p=0.1	

* = *significant*

Legend to Figure 2 (p.39):
IL-6 (<50 pg/ml):
at start n=45;
at 36 months n=20
IL-6 (≥50 pg/ml):
at start n=15;
at 36 months n=5
β2M (<3 mg/l):
at start n=15;
at 36 months n=10
β2M (≥3 mg/l):
at start n=45;
at 36 months n=15
NCAM (<20 U/ml):
at start n=29;
at 36 months n=17
NCAM (≥20 U/ml):
at start n=31;
at 36 months n=8

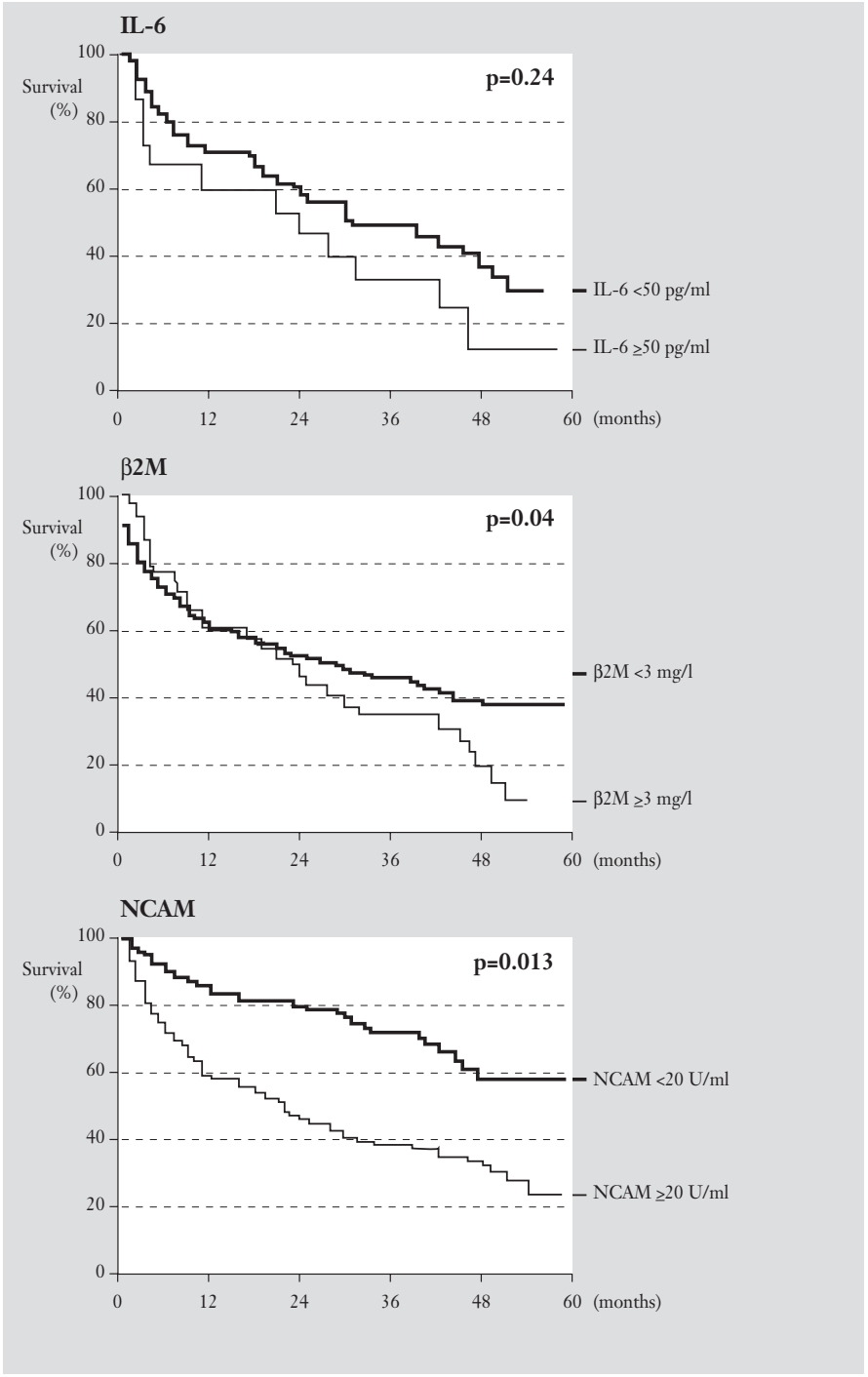

Figure 2. **Survival curves of patients with MM according to high or low values in respectively IL-6, β2M and NCAM.**

Discussion

In this group of well-defined patients with newly diagnosed paraproteinaemia serum IL-6 did not discriminate between the different diagnostic groups. Median serum IL-6 levels were higher in MGUS compared to MM although this difference disappeared when all patients with a documented infection or fever were excluded. As far as the prognostic role of serum IL-6 in MM is concerned, we are in agreement with Kyrtsonis[7] and could not demonstrate the usefulness of serum IL-6 as a prognostic factor which is in contrast with others[8-10]. The established prognostic serum parameters β2M[11] and NCAM[12;13] were both prognostic factors in the CCCW multiple myeloma patients. This underlines that we selected a representative group of patients for this serum IL-6 study.

Studies on serum IL-6 in paraproteinaemia differ in many aspects hampering comparisons with our own IL-6 data (Table 3). Firstly, uniformity in the patient-populations studied is lacking. The patients were either treatment-naive, had received treatment before or were undergoing treatment when serum IL-6 was measured.

Table 3. **Overview of published serum IL-6 investigations in patients with paraproteinaemia.**

Author	Patients (N)*	Time#	Serum IL-6 upper reference limit (URL) and range in pg/ml, differences in (median) serum IL-6 levels among groups
Bioassay			
Bataille *et al*, 1989	MGUS (22), SMM (130), MM (85), PCL (11)	AD/DT	URL: 5, (0-700). Elevated IL-6 in 100% of PCL, 35% of MM and 3% of patients with MGUS or SMM. Elevated levels in 60% of patients with progressive MM or at relapse.
Reibnegger *et al*, 1991	MM: I (13), II (12), III (16)	AD	URL: not given, (1.0-12.5). Rise of IL-6 in advanced disease.
Ludwig *et al*, 1991	MGUS (5), MM: I (13), II (12), III (16), PCL (1)	AD	URL: 7, (0-30). Rise of IL-6 in advanced disease. Elevated levels associated with poor survival.
Nachbaur *et al*, 1991	MGUS (24), MMI/MGUS (24), MM II/III (23), MPS (8), NHL (25), normal (10)	AD/DT	URL: 5, (1-33). Elevated IL-6 in 42% of MM and 13% of MGUS vs normal controls. Rise of IL-6 in advanced and progressive disease. No difference in IL-6 between MGUS and MM I.
ELISA and Bioassay			
Kiss *et al*, 1994	MM (63), MGUS (8), normal (25)	AD/DT	URL: 5 (ELISA), (0-107 ELISA; 0-823 bioassay). IL-6 in MM equivalent to normal controls (ELISA). Discrepancy of bioassay vs ELISA, 15 negative by ELISA tested positive by bio-assay.
Thaler *et al*, 1994	MGUS (57), SMM (7), MM: I (39), II/III (25); normal (40)	AD/DT	URL: not given, (<3-35). No difference in IL-6 between MM I and MGUS. Higher IL-6 in MGUS vs normal, and in advanced or progressive MM.

(Table 3)

ELISA			
Brown *et al*, 1991	MM (34), normal (8)	AD/DT	URL: not given, (200-8200). No difference in IL-6 between MM (all disease stages) and normal controls.
Ballester *et al*, 1992	MM (60)	AD/DT	URL: not given, (80-18,800). IL-6 detectable only in 6/60 patients with MM.
Greco *et al*, 1992	MGUS (45), MM (51), solid tumour (8 colon cancer, 8 melanoma), infections (20), normal (30)	not given	URL: not given, (not detectable-164). Wide and overlapping ranges of IL-6 in all groups. No discriminatory value.
Merico *et al*, 1993	MGUS (6), MM: I (12), II (3), III (15); normal (24)	AD/AR	URL: 100, (120, 4 patients). Elevated IL-6 in 4/30 patients with MM.
Tienhaara *et al*, 1994	MM: I (5), II (13), III (12)	AD	URL: 3300, (<400-43,900); elevated IL-6 in 30%, association with poor survival (only in univariate analysis).
Ballester *et al*, 1994	MM (30), normal (20)	AD/DT	URL: not given, (0-3,360). IL-6 detectable in only 3/27 patients with MM.
Greco *et al*, 1994	MM (39), MGUS+solid tumour (76), MGUS-solid tumour (22)	not given	URL: not given, (0.1-397). IL-6 in MM > MGUS without a solid tumour (MGUS-tumour). No difference in IL-6 between MM and all MGUS (with and without solid tumour).
Pelliniemie *et al*, 1995	MM: I (57), II (100), III (52)	AD	URL: 3.2, (0.4-107). Rise of IL-6 in advanced disease and associated with poor survival.
Fillela *et al*, 1996	MGUS (22),SMM (5), MM (46), normal (30)	AD/DT	URL: 5, (<2-210). Elevated IL-6 in 3% of normal controls, 14% of MGUS, 20% of SMM, 22% of MM at diagnosis, 12% of MM at plateau phase and 92% of MM with progressive disease.

(Table 3)

Kyrtsonis *et al*, 1996	MM: I (3), II (34), III (17); normal (25)	AD	URL: not given, (0-800). Elevated IL-6 in MM vs normal controls. Rise of IL-6 in advanced disease or at relapse and decrease on response to therapy. No correlation with survival.
Cohen *et al*, 1998	Monoclonal gammopathy (106), Control (1626)	AD	URL: not given. Population based study, no diffrence in IL-6 between monoclonal gammopathy and controls.
Schaar *et al*, 1998	IMM (9), MM: I (13), II (4), III (34); MGUS (54), lymphoprol (39), myeloprol (9), solid tumour (35), auto-immune (15)	AD	URL: not given, (6-1,990). No discriminatory role in paraproteinaemia nor a prognostic role in MM.
RIA			
Petterson *et al*, 1992	MM (16), MGUS (12), CLL (9), prim. Sjögren's syndrome (22), normal (32)	AD	URL: 20, (0-(750). Higher IL-6 in MGUS and primairy Sjögren's syndrome vs MM, CLL and normal controls.
Solary *et al*, 1992	MGUS (28), MM (55), WM (19), AML (13), ALL (5), HL (8), NHL (24), CD (2), normal (66)	AD	URL: not given, (113-8,887). Low IL-6 in CD and normals. Higher IL-6 in all other categories, no difference in IL-6 between MM, MW and MGUS. No discriminatory value.
DuVillard *et al*, 1994	MGUS (128), MM (66), WM (27), NHL (11), CLL (7)	AD	URL: 335, (53 - 2464). Elevated IL-6 in 45% of NHL, 35% of MM and 15% of MGUS patients, no predictive value of IL-6 in paraproteinaemia.

*) Patients; abbreviations used: SMM: smouldering MM; PCL: plasma cell leucaemia; NHL: non Hodgkin's lymphoma; HL: Hodgkin's lymphoma; CD: Castleman's disease; CLL: chronic lymphocytic leukaemia; WM: Waldenström's macroglobulinaemia; AML: acute myeloid leukaemia; ALL: acute lymphatic leukaemia. # Time: Time of IL-6 determinations; abbreviations used: AD: at diagnosis; DT: during therapy; AR: at relapse.

Secondly, cut-off values for the upper normal IL-6 level in serum were either not given[7;14-17] or ranged widely from 3.2 pg/ml[10] to 3,300 pg/ml[9]. Each study reported a different range of values, even for normal controls (Table 3).
Thirdly, and perhaps this is the most important, serum IL-6 was either determined by bio-assay or immuno-assay (i.e. radio-immunoassay (RIA) or enzyme-linked-immunoassay (ELISA)). Studies using a bioassay[8;18-20] all found a correlation between serum IL-6 and disease stage in MM. High values were found in MM compared to normal controls or patients with MGUS, and levels were higher in advanced disease. As the final result measured in bioassays is the interaction of several biological activators and inhibitors these tests could be lacking in specificity. Immunoassay methods (ELISA, RIA) were therefore developed to measure more specifically the amount of immunoreactive IL-6. Two studies used both a bioassay as well as an ELISA[16;21]. Thaler *et al* confirmed a good correlation between both assays though Kiss *et al* reported 15 samples being positive by bioassay which were all negative by ELISA. Subsequent studies using only immunoassay methods reported conflicting results. Serum IL-6 levels in MM varied from undetectable to clearly related with advanced disease, and comparisons with normal controls, patients with MGUS or primary Sjögren's syndrome also yielded discrepancies not easily explained[7;9;10;14;22-29]. Epitopes on circulating IL-6 can be protected from binding to monoclonal antibodies by binding to α-2 macroglobulin or the soluble IL-6 receptor (sIL-6R) (Brown *et al*, 1991). This 'immunoassay-shielded IL-6' could well retain its biological activity and be measured in a bioassay though not in an immunoassay. Recently, knowledge on the role of sIL-6R in MM has grown considerably giving a diverse though complicated picture[30]. The biological effect of IL-6 is influenced by sIL-6R and the IL-6/sIL-6R complex could amplify the effect of serum IL-6. Serum IL-6R levels are higher in patients with MM compared to MGUS making it a promising discriminatory marker[31].
Fourthly, IL-6 has other biologic activities such as induction of acute phase proteins[32]. Thus, IL-6 being a pleiotropic cytokine, is also elevated during inflammation and/or infection making it important to exclude all patients with any diagnosis that influences the acute phase response when comparing patients with MM or MGUS to patients in other diagnostic categories. We observed high serum IL-6 levels in patients with MGUS. It is important to look at the definition 'MGUS' which is widely used in the literature[4]. In most published studies on paraproteinaemia the absence of clinical evidence for a haematological malignancy has been accepted as a definition of MGUS. Greco[15] already demonstrated the importance of clearly defining patients with MGUS because the presence of a solid tumour markedly influenced the serum levels of IL-6, CRP and β2M in patients with paraproteinaemia diagnosed as 'MGUS', which could also be demonstrated by us.
In conclusion, although IL-6 is an important cytokine as far as the pathogenesis of MM is concerned, the IL-6 serum value is a poor diagnostic marker in patients with paraproteinaemia and an unreliable prognostic marker in MM.

Reference list

1. Kyle RA. 'Benign' monoclonal gammopathy – after 20 to 35 years of follow-up. Mayo Clin Proc 1993;68:26-36.
2. Klein B, Zhang XG, Lu ZY, Bataille R. Interleukin-6 in human multiple myeloma. Blood 1995;85:863-872.
3. Ong F, Kaiser U, Seelen PJ et al. Serum neural cell adhesion molecule differentiates multiple myeloma from paraproteinemias due to other causes. Blood 1996;87:712-716.
4. Ong F, Hermans J, Noordijk EM et al. A population-based registry on paraproteinaemia in The Netherlands. Comprehensive Cancer Centre West, Leiden, The Netherlands. Br J Haematol 1997;99:914-920.
5. Lymphoma Tumor Group. Plasma cell disorders. British Columbia Cancer Agency. Cancer Treatment Policies , 4-6. 1992.
6. Ong F, Hermans J, Noordijk EM, Kluin-Nelemans JC. Is the Durie and Salmon diagnostic classification system for plasma cell dyscrasias still the best choice? Application of three classification systems to a large population-based registry of paraproteinemia and multiple myeloma. Ann Hematol 1995;70:19-24.
7. Kyrtsonis MC, Dedoussis G, Baxevanis C, Stamatelou M, Maniatis A. Serum interleukin-6 (IL-6) and interleukin-4 (IL-4) in patients with multiple myeloma (MM). Br J Haematol 1996;92:420-422.
8. Ludwig H, Nachbaur DM, Fritz E, Krainer M, Huber H. Interleukin-6 is a prognostic factor in multiple myeloma (letter). Blood 1991;77:2794.
9. Tienhaara A, Pulkki K, Mattila K, Irjala K, Pelliniemi TT. Serum immunoreactive interleukin-6 and C-reactive protein levels in patients with multiple myeloma at diagnosis. Br J Haematol 1994;86:391-393.
10. Pelliniemi TT, Irjala K, Mattila K et al. Immunoreactive interleukin-6 and acute phase proteins as prognostic factors in multiple myeloma. Blood 1995;85:765-771.
11. Bataille R, Grenier J. Serum Beta-2-microglobulin in multiple myeloma. A critical review. Eur J Clin Oncol 1987;23:1829-1832.
12. Kaiser U, Jaques G, Havemann K, Auerbach B. Serum NCAM: A potential new prognostic marker for multiple myeloma (letter). Blood 1994;83:871-873.
13. Kaiser U, Oldenburg M, Jaques G, Auerbach B, Havemann K. Soluble CD56 (NCAM): a new differential-diagnostic and prognostic marker in multiple myeloma. Ann Hematol 1996;73:121-126.
14. Brown R, Joshua D, Uhr E, Snowdon L, Gibson J. The use of a commercially available immunoassay to determine the level of interleukin-6 in the serum of patients with myeloma. Leuk Lymphoma 1991;5:151-155.
15. Greco C, Ameglio F, Alvino S et al. Selection of patients with monoclonal gammopathy of undetermined significance is mandatory for a reliable use of interleukin-6 and other non-specific multiple myeloma markers. Acta Haematol 1994;92:1-7.
16. Thaler J, Fechner F, Herold M, Huber H. Interleukin-6 in multiple myeloma:correlation with disease activity and Ki-67 proliferation index. Leuk Lymphoma 1994;12:265-271.
17. Cohen H.J., Crawford J, Rao MK, Pieper C.F., Currie M.S. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. Am J Med 1998;104:439-444.
18. Bataille R, Jourdan M, Zhang XG, Klein B. Serum levels of interleukin 6, a potent myeloma cell growth factor, as a reflect of disease severity in plasma cell dyscrasias. J Clin Invest 1989;84:2008-2011.

19. Nachbaur DM, Herold M, Maneschg A, Huber H. Serum interleukin-6 in multiple myeloma and other hematological disorders: correlation with disease activity and other prognostic parameters. Ann Hematol 1991;62:54-58.
20. Reibnegger G, Krainer M, Herold M et al. Predictive value of interleukin-6 and neopterin in patients with multiple myeloma. Cancer Res 1991;51:6250-6253.
21. Kiss TL, Lipton JH, Bergsagel DE et al. determination of IL6, IL1 and IL4 in the plasma of patients with multiple myeloma. Leuk Lymphoma 1994;14:335-340.
22. Ballester OF, Corrado C, Moscinski LC, Bruno S, Burgess J. Clinical significance of serum interleukin (IL-6) levels in patients with multiple myeloma (MM). Proceedings of Asco 1992;11:98.
23. Greco C, Vitelli G, Cianculli AM et al. Are serum interleukin-6 levels always useful for differentiating monoclonal gammopathies in unselected patients ? Blood 1992;79:2173-2174.
24. Petterson T, Metsärinne K, Teppo A-M, Fyhrquist F. Immunoreactive interleukin-6 in serum of patients with B-lymphoproliferative diseases. J Int Med 1992;232:439-442.
25. Solary E, Guiguet M, Zeller V et al. Radioimmunoassay for the measurement of serum IL-6 and its correlation with tumour cell mass parameters in multiple myeloma. Am J Hematol 1992;39:163-171.
26. Merico F, Bergui L, Gregoretti MG et al. Cytokine involved in the progression of multiple myeloma. Clin Exp Immunol 1993;92:27-31.
27. Ballester OF, Moscinsky LC, Lyman GH et al. High levels of interleukin-6 are associated with low tumor burden and low growth fraction in multiple myeloma. Blood 1994;83:1903-1908.
28. DuVillard L, Guiguet M, Casasnovas R et al. Diagnostic value of serum IL-6 level in monoclonal gammopathies. Br J Haematol 1995;89:243-249.
29. Filella X, Bladé J, López Guillermo A et al. Cytokines (IL-6, TNF-a, IL-1a) and soluble interleukin-2 receptor as serum tumor markers in multiple myeloma. Cancer Detect Prev 1996;20:52-56.
30. Treon SP, Anderson KC. Interleukin-6 in multiple myeloma and related plasma cell dyscrasias. Curr Opin Hematol 1998;5:42-48.
31. Stasi R, Brunetti M, Parma A et al. The prognostic value of soluble interleukin-6 receptor in patients with multiple myeloma. Cancer 1998;82:1860-1866.
32. Kishimoto T. The biology of interleukin-6. Blood 1989;74:1-10.